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Acute COVID-19 Infection Impact on Patients Receiving Opiate Agonist Treatment with Methadone

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ABSTRACT

Background: During the COVID-19 epidemic in Georgia, to control the infection and prevent further spread of the SARS-CoV-2 virus among methadone replacement therapy (MRT) users, the State program with methadone for opioid drug addiction has been implemented since 2009, and in March 2020, switched to the take-home dose regimen countrywide.

Objectives: This study aimed to determine the morbidity and mortality rates of COVID-19 in MRT recipients from March 2020 to July 2022.

Methods: A case series study was conducted in the country. A retrospective analysis of COVID-19 surveillance data was performed. Study subjects were selected based on the following criteria: age between 21 and 65, male gender, MRT recipient for at least three months, and laboratory-confirmed (positive PCR test for SARS-CoV-2 virus antigen) COVID-19 infection. Descriptive statistics were applied to the study results.

Results: The study results showed that the incidence of COVID-19 was increasing among MRT recipients over the pandemic years, ranging from 58.6 per 10,000 in 2020 to 30.6 per 10,000 in 2022; however, the number of death cases was rare. By contrast, during the epidemic years, 22 cases of death were reported in MRT users, while in the general population, death cases were frequent, exceeding 2,200. The mortality rate was 1.5 times lower in the study subjects than in the general population.

Conclusions: The study findings indicate a high incidence of SARS-CoV-2 viral infection in MRT recipients; however, cases of reinfection, case fatality rates, and mortality rates were lower compared to those in the general population during the COVID-19 pandemic. Further research is required to understand the mechanism of interaction between COVID-19 and methadone, to maintain MRT efficacy and control and manage COVID-19 and similar severe respiratory infections in MRT recipients.

Keywords: COVID-19; incidence; methadone replacement therapy (MRT); mortality; reinfection.

BACKGROUND

At the beginning of the COVID-19 pandemic, it was assumed that SARS-CoV-2 virus infection would disproportionately impact drug addicts due primarily to their associated health problems. It has been found that individuals with Substance Use Disorders (SUDs) are more likely to develop respiratory complications and cardiovascular disease.[1] Drug addicted individuals may also have underlying medical conditions that put them at increased risk for severe illness from COVID-19.[2] Slowed breathing due to opioids causes hypoxemia, which can lead to cardiac, pulmonary, and brain complications.[3] Opioids depress respiratory drive, and long-term use is immunosuppressive.[4,5] COVID-19 is at a higher risk in patients who use opiates, which impairs the cells of the innate and adaptive immune system, leading to more hospitalizations in this subgroup.[6] Several studies showed that people with substance use disorders are at increased risk of severe illness and death from COVID-19.[7-11] An infection may be even more dramatic in those patients who misuse or chronically use opioids and are likely to be characterized by immune and/or respiratory depression.[12,13] Opiate users may misinterpret COVID-19 symptoms as opioid withdrawal and treat them by self-administering opioids.[14] Another important issue to consider when discussing the acute effects of COVID-19 on SUDs is the opposite relationship. This means exploring the increased susceptibility of COVID-19 in patients who are suffering from SUDs.[14] Hospitals, already overburdened to manage this health disaster, are being pushed further away, even if they come with symptoms of COVID-19 and similar illnesses.[14,15] The current coronavirus disease 2019 (COVID-19) pandemic and ''opioid epidemic/pandemic" have intersected and interacted with each other to impose a greater public health threat.[12,13] Along with negatives, opioids have predictable analgesic actions. They are widely used in many clinical settings. Still, they also produce unwanted side effects, including respiratory depression, tolerance, and are misused; however, the use of opioids, including methadone, as a cough suppressant is long established.[16] Eagleton M. et al. indicate that patients treated with opioid substitution treatment may already have a respiratory burden.[17] However, it is remarkable that so few have presented with signs or symptoms of COVID-19.[17] The studies have also suggested that methadone, like other long-acting opioids, can positively influence the immune

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system and restore cytokine expression, probably due to the activation of the mu-opioid receptor.[18]

Georgia is one of the most affected countries in the world by the epidemic of SARS-CoV-2 viral infection.[19] The impact of the COVID-19 epidemic was tremendous on the entire population, including vulnerable groups, especially drug users. Since 2009, Georgia has been implementing a substitution treatment State program with methadone for opioid drug addiction. At the very beginning of the COVID-19 epidemic in March 2020, to combat the spread of the infection, it legally switched to dispensing take-home doses to the MRT recipients.

Epidemiological characteristics of the COVID-19 epidemic in Georgia

The first confirmed case of COVID-19 in Georgia was recorded on February 26, 2020.[19] The highest number of cases in the country since the start of the pandemic was recorded during the second wave in 2020. As of July 15, 2022, 1,673,160 cases were officially confirmed. The 14-day cumulative incidence was 3,251 per 100,000 of the population. The reproduction index was 1.6. The 7-day mortality rate was 0.3 per 1,000,000 population, and the lethality during the entire pandemic period was 1%. During the wave caused by the highly virulent delta variant in Georgia in August 2021, the 14-day cumulative incidence reached its peak at 1,798 per 100,000 population. Due to the high virulent nature of the variant, the rate of complications and hospitalization was also high (>15%).

Since January 2022, the Omicron variant has been the dominant strain in the country; compared to the Delta variant, the rate of hospitalization has decreased. Following the spring period of 2022, an increase in the number of COVID-19 cases was observed in Georgia, as indicated by the epidemic parameters of incidence, reproduction index, and positive test rate. Despite the increase, the global death rate remained relatively stable. Overall, six waves of the epidemic were recorded countrywide. Lockdowns and other restriction measures were implemented in all regions of the country since the outbreak of the epidemic.

METHODS

A descriptive case series study was conducted in the country. Retrospective analysis of COVID-19 surveillance data obtained from the National Center for Disease Control and Public Health (NCDC) was performed for the period March 2020 to July 2022. Study subjects were selected from all regions of the country based on the following criteria: age between 21 and 65, male gender, receipt of MRT for at least three months, and a positive PCR test for SARS-CoV-2 virus antigen. Results were compared to those of the general population, using the following selection criteria: an age range of 21 to 65 and male gender. Descriptive statistical analysis was performed in Microsoft Excel and IBM SPSS Statistics.

RESULTS

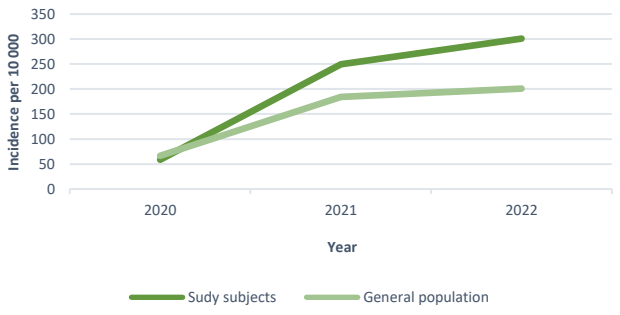
The study findings showed that the number of SARS-CoV-2 infections increased over the analyzed period in Methadone Replacement Therapy (MRT) recipients (mean age = 43.01 ± 9.39) as well as in the general population (mean age = 40.9 ± 0.03) (Tab.1). Every third person in MRT users contracted laboratory-confirmed COVID-19 during the six waves of the epidemic.

TABLE 1. Number of cases of COVID-19 in MRT recipients and the general population aged 21-65

Year	MRT Recipients, Number (%)	General Population, Number (%)
2020	602 (5.9)	71429 (6.5)
2021	2929 (24.9)	195907 (18.2)
2022	3731 (30.6)	212253 (19.9)

The morbidity level with COVID-19 infection was significantly higher in the study population (ranging from 58.6 in 2020 to 306.3 in 2022 per 10,000) compared with the general population of the target ages (ranging from 66.5 to 200.9 per 10,000) during the analyzed period. An upward trend was observed in both groups (Fig. 1). Although the incidence rates and proportions of infected persons among MRT recipients exceeded those in the general population, disease severity in the study subjects did not necessitate hospitalization. In contrast, in the general population, due to the severity of the infection, over 10.00% of infected persons were hospitalized.

FIGURE 1. Incidence of COVID-19 in MRT recipients and the general population during the COVID-19 epidemic



Our findings are consistent with the studies indicating that persons with SUD and Opiate Agonist Treatment (OAT) users are typically a high-risk and marginalized, vulnerable

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population for all infections and are invariably more prone to contracting infection during the COVID-19 pandemic.[1,7,8,20] It is crucial to recognize that, like other opioids, methadone significantly elevates the levels of brain-derived neurotrophic factor in heroin-dependent patients. Furthermore, those undergoing methadone treatment attain a balanced state that reduces oxidation.[21] It is well established that oxidative stress is directly associated with unfavorable outcomes in critically ill COVID-19 patients, representing a critical pathway to multi-organ failure.[22] All these factors should be considered when observing the high incidence of COVID-19 among MRT users.[23] Additionally, since opiate users may misinterpret COVID-19 symptoms as opioid withdrawal and treat it by self-administering opioids, we consider that this could lead to under-reporting of COVID-19 infection in the study subjects, given that those dependent on drugs are also likely to be more vulnerable to the effects of this virus.[14,24]

Although the incidence rates of COVID-19 in our study population showed an upward trend, the overall case fatality rate was 1.5 times lower in MRT recipients than in the general population (Tab.2).

TABLE 2. Case mortality rate from SARS-CoV-2 infection in MRT recipients and the general population

Year	Study Subjects, Number (%)	General Population, Number (%)
2020	1 (0.16)	463 (0.65)
2021	13 (0.44)	1485 (0.79)
2022	6 (0.16)	268 (0.12)
Total	20 (0.27)	2216 (0.46)

Consequently, mortality rates in study subjects were lower during the epidemic years, ranging from 0.10 to 1.12 per 10,000, compared with the general population, whose mortality rates ranged from 0.43 to 1.40 per 10,000. Similar findings were described by Aldabergenov D.et al.[25], indicating that methadone-related deaths in non-prescribed individuals, but not prescribed individuals, increased considerably above the annual trend forecast for 2020 during the first COVID-19 lockdown in England. Eagleton M. et al. in their study[17] showed that in 11,223 patients taking an opioid substitution treatment by the end of July 2020, there were fewer than 20 cases of COVID-19 reported among patients taking an opioid substitution treatment. Cases were usually mild, clinical manifestations of the infection were rare, and no deaths from COVID-19 were reported, even among severely ill individuals.

Although no evidence has been found in the reviewed literature regarding reinfection with the SARS-CoV-2 virus in COVID-19 patients, our findings showed that reinfection with the SARS-CoV-2 virus after 60 days since the index case was comparably rare in MRT recipients compared to the general population (Tab.3).

TABLE 3. Reinfection with SARS-CoV-2 in MRT recipients and the general population

Year	Study subjects, number (%)	General population, number (%)
2020	0 (0)	21 (0.1)
2021	34 (1.16)	2734 (1.4)
2022	449 (12.03)	35829 (16.88)

DISCUSSION

We agree with some researchers that currently, there is a lack of evidence on the effect of therapeutic opioids on patients with COVID-19, as well as whether they influence outcomes among patients with COVID-19 infection.[7,24]

Based on our study findings and the literature review we consider that some controversial study results in the reviewed literature might be the reflection of several factors (including confounding) such as variation in: study design, study population, selection method of study subjects, the pandemic period for the study, treatment duration, frequency and number of take-home doses, etc.

It is remarkable that in the reviewed literature, there are controversial data and predictions regarding the COVID-19 impact on people with SUDs, including users of methadone maintenance treatment (MMT)[22,25], ranging from no effect or negative to protective. For instance, Wang et al., in their retrospective case-control study, showed that medications used to treat opioid use disorders (OUDs) like methadone, buprenorphine, and naltrexone did not affect SUD patients' risk for COVID-19, especially those with a recent SUD diagnosis.[25] Some authors conclude that the impact of the epidemic on MMT-receiving patients has been negative, which has increased the patients' craving for drugs and the risk of overdose death26 or relapse.[2,13,26,27] Eagleton M. et al. postulated that OAT has a protective effect on the clinical manifestations of COVID-19 and called for further research on this.[17] Owiti JA et al.[26] in their study noted that methadone and buprenorphine are safe among patients positive for COVID-19 and that the medications on their own did not lead to adverse outcomes among patients with COVID-19. The results also show that patients with OST are not at an increased risk of deterioration from COVID-19 infection.[7,26] Recent Irish research decisively demonstrates that COVID-19 infection rates among individuals receiving opiate agonist treatment (OAT) - which includes methadone and similar medications for opioid addiction - are significantly lower than expected. This strongly indicates that these individuals have either had

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minimal exposure to the virus or have reported fewer cases of COVID-19 overall.[8,28] Overall, our findings contribute to the understanding of the impact of COVID-19 on MRT recipients and highlight the need for further research to clarify the relationship between opioid treatment and COVID-19 outcomes.

CONCLUSIONS

Incidence of SARS-CoV-2 virus infection was high in MRT recipients; however, cases of reinfection and death, as well as mortality rates, were low during the COVID-19 epidemic in the country.

Along with other issues, such as the effects of SUD recovery status on COVID-19 infection, hospitalization, and death risk, safety and protective property of methadone on infectivity with and outcome of the respiratory infection, we consider that further research is required on the mechanism of the interaction between SARS-CoV-2 virus and methadone to control MRT efficacy and manage COVID-19 and similar severe respiratory infections in MRT recipient population during outbreaks and epidemics.

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